2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO SELENIUM IN THE UNITED STATES

Selenium is an essential micronutrient for humans and animals that is found ubiquitously in the environment, being released from both natural and anthropogenic sources. The principal release of selenium into the environment from anthropogenic sources is from coal combustion. Natural sources of selenium include the weathering of selenium-containing rocks and soils, and volcanic eruptions. Selenium is found in most rocks and soils, and naturally occurs at low concentrations in surface waters and groundwaters of the United States. Accumulation of selenium in agricultural drainage waters has been documented in basins in the western United States, particularly in California. Ambient background concentrations of selenium in the air are very low, generally in the nanogram per cubic meter (ng/m^3) range.

Exposure of the general population to selenium is primarily by ingestion of its organic and inorganic forms, both of which occur naturally in the diet. The greatest portion of dietary intake occurs from organic forms of selenium, mainly the amino acids selenomethionine and selencysteine, in grains, cereals, and forage crops. The main inorganic sources of selenium in the diet are selenate and selenite, which are less absorbed than the organic forms. Other exposure pathways for selenium, which are of lesser importance, are water and air. Various estimates of the selenium intake for Americans have ranged from 0.071 to 0.152 mg selenium/day (approximately 1–2 μg/kg/day in adults). Some people living in areas with high soil concentrations of selenium (as in areas of the western United States) might have higher exposure because of the natural selenium levels found locally, particularly if they consume crops primarily grown in that area. Metal industry workers, health service professionals, mechanics, and painters may be exposed to higher levels of selenium than the general population or workers employed in other trades.

2.2 SUMMARY OF HEALTH EFFECTS

As an essential trace element in humans and animals, selenium is a biologically active part of a number of important proteins, particularly enzymes involved in antioxidant defense mechanisms (e.g., glutathione peroxidases), thyroid hormone metabolism (e.g., deiodinase enzymes), and redox control of intracellular

reactions (e.g., thioredoxin reductase). Depending upon the level of intake, selenium can have nutritional or possibly toxic effects. Most people in the United States are unlikely to suffer from selenium deficiency. Although excessive intake of selenium can cause adverse health effects, these are generally observed at doses more than 5 times greater than the Recommended Dietary Allowance (RDA).

The current RDA for selenium, established by the Food and Nutrition Board of the National Research Council (National Academy of Sciences), is 55 µg/day for male and female adults (approximately 0.8 µg/kg/day). This recommendation represents a decrease from the previous RDA of 70 µg/day for males; 55 µg/day was already the RDA for females. The current NAS Tolerable Upper Intake Level (UL) for selenium is 400 µg/day for adults (approximately 5.7 µg/kg/day). At the time that the RDA was in the process of being reevaluated (i.e., late 1990s), selenium was found to have entered the environment from old mining operations in some northwestern U.S. locations. This resulted in public concern about the potential effects of selenium on livestock grazing in the vicinity, and ultimately possible effects in humans consuming food products from plants and animals raised in those areas. The combination of the increased concern regarding selenium toxicity and the reduction in the selenium RDA indicated to ATSDR that an Agency reevaluation of selenium from a toxicological perspective is warranted; the previous version of the ATSDR Toxicological Profile for Selenium was published in 1996.

Although selenium deficiency is not a health issue in the United States, it has been associated with two endemic diseases found in selenium-poor regions of China: a cardiovascular condition known as Keshan Disease and an osteoarthropathy called Kashin-Beck Disease. Keshan Disease is a cardiomyopathy characterized by cardiac enlargement, abnormal ECG patterns, cardiogenic shock, and congestive heart failure, with multifocal necrosis of the myocardium. The disease is reported to occur primarily in children and women of child-bearing age and has been successfully treated by selenium supplementation; however, a low incidence of cases persisting after selenium supplementation suggests that there may be other contributing factors. The evidence for the involvement of selenium in Kashin-Beck disease is less clear than for its involvement in Keshan disease. Kashin-Beck Disease is characterized by atrophy, degeneration, and necrosis of cartilage tissue, and occurs primarily in children between the ages of 5 and 13 years; it also has been successfully treated with selenium supplements. Chronically ill people and older people have been shown to have lower organ concentrations of selenium than healthy individuals, but it is not clear if this is a cause or consequence of aging or illness.

Relatively little information is available on health effects of elevated inhalation levels of selenium. The primary target organ in humans and laboratory animals in cases of acute, high-level inhalation exposure to

selenium dusts or fumes is the lung, with cardiovascular, hepatic, nervous, and renal involvement as well. Lesser effects are observed in other organs/organ systems. Workers acutely exposed to high concentrations of elemental selenium dust have reported stomach pain and headaches, whereas workers briefly exposed to high levels of selenium dioxide dust experienced respiratory symptoms such as pulmonary edema, bronchial spasms, symptoms of asphyxiation and persistent bronchitis, elevated pulse rates, lowered blood pressure, vomiting, nausea, and irritability. No information is available on health effects in humans or laboratory animals from intermediate-duration (up to 1 year) inhalation exposure to selenium or selenium compounds. Regarding chronic inhalation exposure, several occupational studies describe respiratory effects such as irritation of the nose, respiratory tract, and lungs, bronchial spasms, and coughing following exposure to selenium dioxide or elemental selenium as dust. Respiratory symptoms similar to those reported for occupationally-exposed humans have been seen in animals inhaling high doses of elemental selenium fumes or dust, and studies of animals with acute inhalation exposure to hydrogen selenide or elemental selenium fumes or dust have reported hepatocellular degeneration and atrophy of the liver.

Acute oral exposure to extremely high levels of selenium (e.g., several thousand times more than normal daily intake) produces nausea, vomiting, and diarrhea in both humans and laboratory animals. Acute oral exposure of humans to selenium has occasionally caused cardiovascular symptoms, such as tachycardia, but no electrocardiographic abnormalities were found in individuals from a human population chronically exposed to selenium. In laboratory animals, acute- and intermediate-duration oral exposure to very large amounts of selenium (approximately 100 times normal human intake) has produced myocardial degeneration in laboratory animals.

Chronic oral intake of very high levels of selenium (10–20 times more than normal) can produce selenosis in humans, the major effects of which are dermal and neurological. As shown by affected populations in China, chronic dietary exposure to these excess levels of selenium has caused diseased nails and skin and hair loss, as well neurological problems, including unsteady gait and paralysis. Additional information on selenosis is summarized in the following subsection of this chapter. In contrast, studies of people living in areas of naturally occurring high selenium concentrations in the United States have not revealed adverse health effects in those populations. This difference may result from a lower (~2-fold) selenium exposure in the U.S. population compared to the Chinese population, as well as a better balanced, higher protein diet in the United States, which could lead to reduced toxicity of selenium through interactions with dietary components.

Intermediate and chronic oral exposure of livestock to high levels of dietary selenium compounds also produces dermal and neurological effects. Studies in rats and other laboratory animals with high selenium tissue concentrations demonstrate that many organ systems retain selenium and are affected. The primary adverse effects in laboratory animals exposed to inorganic selenium salts or to selenium-containing amino acids are cardiovascular, gastrointestinal, hematological, hepatic, dermal, immunological, neurological, and reproductive, although doses causing these effects are generally at least 5 times higher than normal daily selenium intake. A condition (syndrome) referred to as "blind staggers" has been repeatedly observed in cattle feeding off vegetation in areas with high selenium content in the soil. However, the neurological effects have not been replicated in experimentally-exposed cattle receiving doses of selenium sufficient to induce hoof lesions, and thus, the neurological signs associated with "blind staggers" may be due to other compounds found within this vegetation.

Some evidence for effects on the endocrine system has also been found following long-term oral exposure to elevated levels of dietary selenium in humans and rats. In humans, blood levels of thyroid T_3 hormone (triiodothyronine) decreased in response to increased dietary selenium for durations of 3 months and longer at intakes several times higher than normal intake, although the hormone levels remained within the normal range. In rats, type-I-deiodinase activity decreased in response to increased exposure to selenium for several months, but the levels of thyroid hormones in these animals did not show a consistent pattern.

Studies of Chinese populations and laboratory animals exposed to high levels of organic and/or inorganic selenium compounds have not found evidence of selective teratogenic effects in mammals.

There is no evidence to support a causal association between selenium compounds and cancer in humans. In fact, some epidemiological and experimental evidence suggests that selenium exposure under certain conditions may contribute to a reduction in cancer risk. The chemopreventive potential of supplemental selenium is currently under research. Selenium sulfide and ethyl selenac are the only selenium compounds that have been shown to be carcinogenic upon oral administration in rodents; however, significant exposure of humans to these chemical forms of selenium is extremely unlikely.

Additional information on main health effects of selenium in humans and animals is summarized below and detailed in Chapter 3.

Selenosis. Following chronic oral exposure to excessive amounts of the organic selenium compounds in food, the two principal clinical conditions observed in humans are dermal and neurological effects, as described most completely in the epidemiological study of endemic selenosis in the People's Republic of China. The dermal manifestations of selenosis include loss of hair, deformation and loss of nails, and discoloration and excessive decay of teeth, while neurological effects include numbness, paralysis, and occasional hemiplegia. The average dietary intake of selenium associated with selenosis in these people has been estimated to be 1,270 µg/day (~0.02 mg/kg/day, or 10–20 times higher than normal daily intake).

Loss of hair and malformation of hooves in pigs, horses, and cattle, and poliomyelomalacia in pigs have been reported to occur following long-term exposure to excessive amounts (more than 30 times the normal dietary amount of selenium) of the organic selenium compounds found in seleniferous plants. Histologically, swine with selenium-induced neurological signs exhibit bilateral macroscopic lesions of the ventral horn of the spinal cord. The selenium in the selenium-accumulating plant *Astragalus bisulcatus* appears to be a more potent neurotoxicant than D,L-selenomethionine or selenate. The form of selenium in *A. bisulcatus* is unknown, although it is apparently nonprotein. Myocardial degeneration has been experimentally produced in cattle, sheep, and swine (as well as in laboratory mammals) by acute and longer-term exposures to inorganic salts of selenium, but it is unclear whether seleniferous grains or forages, or other natural sources of selenium, cause the same cardiomyopathy.

The neurological signs and histopathology observed in livestock following oral exposure to excess selenium compounds have not been recorded in laboratory animals. This suggests that (1) small laboratory mammals might not be appropriate models for selenium toxicity in humans due to toxicokinetic differences (e.g., laboratory animals absorb selenium compounds to a lesser extent, or metabolize and/or excrete selenium compounds more quickly), (2) some as yet unidentified organic form of selenium contributes to the neurological manifestations of chronic selenosis in humans and in livestock, (3) unrecognized confounding factors, such as other plant toxins, have contributed to the neurological syndrome associated with chronic selenosis in field studies of humans and livestock, and/or (4) species differences in interactions between selenium and other nutrients or xenobiotics, such as vitamin E and methionine, which have been found to be antagonistic to selenium toxicity

Endocrine Effects. Selenium is a component of all three members of the deiodinase enzyme family, the enzymes responsible for deiodination of the thyroid hormones, and has a physiological role in the

control of thyroid hormone levels. Significant decreases in serum T_3 hormone levels have been observed in humans that were environmentally or experimentally exposed to elevated dietary levels of selenium (several times higher than normal). However, the T_3 hormone levels observed in these studies were still within the normal human range, so the biological impact of this change is unclear. The effect of increased dietary selenium on other thyroid hormones is also uncertain. Intermediate-duration studies in rats show a decrease in type-I-deiodinase activity in response to elevated selenium; however, the levels of thyroid hormones in these animals did not show any consistent changes.

Reduced growth rate of young animals and weight loss in older animals are two of the most common effects in experimental animals following long-term oral intake of excessive levels of inorganic and organic compounds of selenium. It is quite possible that selenium-induced reduction in growth has a thyroid or other endocrine component. For example, selenite treatment of young rats decreased somatomedin C levels, although somatomedin C was not a sensitive index of elevated selenium exposure in humans from a high-selenium area of South Dakota, and growth hormone secretion in response to the growth hormone releasing factor was also reduced in selenium-treated rats. The primary endocrine target of selenium leading to decreased growth has yet to be elucidated. Pancreatic toxicity has been observed following excess selenium exposure. Cytoplasmic flocculation was observed in lambs treated with a single oral dose of selenite, and pancreatic damage, which was not further described, was noted in rats following chronic oral treatment with selenate or selenite. Pancreatic toxicity associated with excessive selenium exposure is likely related to the unique ability of that organ to accumulate the element.

Reproductive Effects. In humans, no correlation has been found between selenium levels in seminal fluid and sperm count or mobility. No significant increase in spontaneous abortions was reported among women chronically exposed to drinking water containing increased selenium, but the concentration was not considered to be unusually high. In animals, oral exposure to high doses of sodium selenate or selenite (at least 8 times greater than those normally supplied by an adequate diet) caused increased numbers of abnormal sperm, as well as testicular hypertrophy, degeneration, and atrophy in male rats, and affected the estrous cycle in female rats and mice. The animals that showed these effects were not mated, so it is not clear if fertility was affected. Oral treatment with L-selenomethionine similarly caused disturbances in the menstrual cycle (anovulation, short luteal and follicular phases) in monkeys. Selenium deficiency has also been reported to cause decreased sperm production and motility in rats. The relevance of the reproductive effects of high and low levels of selenium in laboratory animals to potential reproductive effects in humans is not known.

Hepatic Effects. Liver effects have not been reported for humans exposed to excessive amounts of selenium. No significant abnormalities were found in blood levels of liver enzymes in people living in high selenium areas, or in liver morphology (ultrasonographic examination) of individuals suffering from severe symptoms of selenosis. In experimental animals and livestock, however, the liver has been shown to be affected following inhalation or oral exposure to different kinds of selenium compounds. Hepatocellular degeneration occurred in guinea pigs following short-term inhalation exposure to excessive levels (hundreds of times higher than normal) of elemental selenium dust (8 mg/m^3) or hydrogen selenide (33 mg/m^3). Cirrhosis, hepatocellular degeneration, and changes in liver enzyme levels in serum have been reported for rats, pigs, and mice orally exposed to selenite, selenate, or organic selenium. The oral doses of selenium producing the various adverse liver effects were approximately 10 times the amount normally found in an adequate diet. Excessive dietary exposure to selenium sulfide (several thousands of times higher than normal selenium intake) produced frank hepatotoxicity in rats, but not in mice. Although the liver appears to be the primary target organ for the oral toxicity of selenium in experimental animals following intermediate and chronic exposure, liver cirrhosis or dysfunction has not been a notable component of the clinical manifestations of chronic selenosis in humans. The lack of evidence of liver damage in humans due to selenosis, despite all of the animal data to the contrary, suggests a problem with the animal models of the disease.

Renal Effects. No reports of renal effects in humans were located. In animals, mild kidney effects have been observed following oral exposure to seleniumat levels several hundred times higher than normal human intake. These effects include hydropic degeneration in sheep following a single dose of 5 mg Se/kg/day as sodium selenite. Rats appear to be more sensitive than mice to renal effects of repeated oral exposures to selenium compounds. A dose-related increase in renal papilla degeneration, described as mild to minimal, was observed in rats at very high levels of selenate or selenite (0.5 mg Se/kg/day, several hundreds of times higher than normal human intake) in the drinking water for 13 weeks, although increased kidney weight was the only renal effect in similarly exposed mice. Mice that were given excessive daily doses of selenium sulfide by gavage (464 mg Se/kg/day for 13 weeks), however, developed interstitial nephritis.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

No MRLs were derived for inhalation exposure to selenium because of insufficient quantitative data concerning both human and animal exposures. Data on the health effects of inhaled selenium in humans are available from studies of occupationally exposed workers (Clinton 1947; Glover 1970; Holness et al. 1989; Kinnigkeit 1962; Wilson 1962). These studies suggest that the respiratory system is the most sensitive end point for inhaled selenium dust, but they do not provide quantitative measurements of exposure levels and are frequently confounded by concurrent exposures to other chemicals. Laboratory animal studies support the respiratory system as the main target of selenium inhalation toxicity (Dudley and Miller 1941; Hall et al. 1951), but the available data are for acute exposures to high concentrations of selenium that also produced serious health effects, including death.

Oral MRLs

No MRLs were derived for acute or intermediate oral exposure to selenium because of insufficient information regarding adverse health effect levels in humans and experimental animals. For acute exposure, no quantitative data are available from studies of humans. Some acute oral animal studies identify lowest-observed-adverse-effect levels (LOAELs) for organ weight changes, behavioral changes, and reduced body weight, but these occur at doses similar to those producing serious LOAELs for paralysis and developmental effects in other mammalian studies.

Information on health effects of intermediate-duration (15–365 days) oral exposure to selenium in humans is mainly available from a 120-day experimental study of men who were exposed to a controlled diet of foods naturally low or naturally high in selenium (Hawkes and Turek 2001; Hawkes et al. 2001). Eleven subjects were fed diets providing selenium intake levels of 0.6 µg/kg/day for 21 days (baseline period), followed by 0.2 µg/kg/day (6 subjects) or 4 µg/kg/day (5 subjects) for the subsequent 99 days. This was more a nutritional study than a toxicological study, as indicated by selenium intake levels that bracketed the current RDA (~0.8 µg Se/kg/day) and were well below the tolerable upper limit (~5.7 µg Se/kg/day) recommended by the Food and Nutrition Board (NAS 2000). Comprehensive evaluations were performed that included serum levels of thyroid hormones (T_3 and TSH) and reproductive hormones (testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, and progesterone), sperm quality indices (number and concentration, motility, forward progression and velocity, and morphology), and immunological end points (including serum immunoglobulin levels, lymphocyte counts

and phenotypes, natural-killer cell activity, proliferative response of lymphocytes to mitogenic stimulation, delayed-type hypersensitivity skin responses to recall antigens, and antibody responses to diptheria-tetanus and influenza vaccines). Effects were essentially limited to subclinical changes in thyroid hormones and sperm motility, which are not considered to be toxicologically meaningful. Serum T_3 concentrations decreased in the high selenium group and increased in the low selenium group, but all values apparently remained within the normal human range. Serum TSH concentrations increased in the high-selenium group with no change in the low-selenium group, but values also remained in the normal range. Sperm motility was slightly lower than the baseline value in the high selenium group at study termination. The decrease in sperm motility cannot be clearly attributed to selenium because the effect was not consistent over the duration of exposure, and is unlikely to be adverse because it is at the low end of the normal range and was not accompanied by any changes in other indices of sperm movement (progression or forward velocity) or sperm numbers or morphology.

Effects in intermediate-duration studies in experimental animals include reductions in liver enzyme activities, changes in liver and body weights, and histological changes in the liver and kidney, but the relevance of these effects to selenium toxicity in humans is questionable. For example, humans with selenosis did not display any changes in serum levels of liver enzymes or morphological damage to the liver, as shown by ultrasonographic examination (Yang et al. 1989a). Further, the liver and kidney effects in animal studies occurred at doses (≥0.2 mg/kg/day) that were considerably higher than the 4 µg/kg/day intake level that caused the subclinical thyroid hormone and sperm motility alterations in humans (Hawkes and Turek 2001; Hawkes et al. 2001). Although the human experimental study identifies a no-observed-adverse-effect level (NOAEL) of 4 µg/kg/day for sensitive endocrine and male reproductive end points, it is an inappropriate basis for derivation of an intermediate oral MRL. In particular, because this is a free-standing NOAEL, proximity to the LOAEL region is not known, and the use of the NOAEL to derive an MRL would yield a value that is in the range of the selenium RDA (approximately 0.8 µg/kg/day) (NAS 2000) and below the chronic oral MRL derived below.

- An MRL of 0.005 mg/kg/day (5 µg/kg/day) has been derived for chronic oral exposure (>365 days) to selenium.

This MRL is based upon a study by Yang and Zhou (1994), who examined of a group of five individuals who were recovering from selenosis, and who were drawn from a larger population from an area of China where selenosis occurred (Yang et al. 1989a, 1989b). The study collected data on selenium levels in the diet, blood, nails, hair, urine, and milk of residents at three sites with low, medium, and high selenium, and compared the incidence of clinical symptoms of selenosis (morphological changes in fingernails)

with dietary intake of selenium and selenium levels in blood. The average adult body weight was 55 kg (Yang et al., 1989b). It was found that selenium levels in blood corresponded to the dietary intake of selenium, and that symptoms of selenosis occurred at or above a selenium intake level of 910 µg/day (0.016 mg/kg/day) (Yang et al. 1989a). In 1992, Yang and Zhou (1994) reexamined five individuals from the high selenium site who had been suffering from symptoms of selenosis (loss of fingernails and hair), but were recovering (nails were regrowing). Since their earlier report, the living conditions of the population had improved; they had been cautioned against consuming high selenium foods, and part of their diet from locally produced corn had been replaced with rice or cereals. Yang and Zhou (1994) found that the concentration of selenium in the blood of these individuals had fallen from 1,346 µg/L (measured in 1986) to 968 µg/L (measured in 1992). Using a regression equation derived from the data in an earlier report (Yang et al. 1989b), it was calculated that the dietary intake of selenium associated with selenosis in these individuals was 1,270 µg/day, while an intake of 819 µg Se/day (was associated with recovery (Yang and Zhou 1994).

The chronic oral MRL is based on a NOAEL of 819 µg/day (0.015 mg/kg/day) for disappearance of symptoms of selenosis in recovering individuals (Yang and Zhou 1994) and uses an uncertainty factor of 3 for human variability. An uncertainty factor of 3 was considered appropriate because the individuals in this study were sensitive individuals drawn from a larger population and because of supporting studies, as discussed in Appendix A. The NOAEL used to derive the MRL is consistent with NOAELs observed for other human populations (Longnecker et al. 1991). The MRL is about 2.5–5 times higher than normal selenium intake levels of 71–152 µg/day (approximately 0.001–0.002 mg/kg/day) (DHHS 2002; FDA 1982a; Levander 1987; Pennington et al. 1989; Schrauzer and White 1978; Schubert et al. 1987; Welsh et al. 1981), and approximately 6 times greater than the RDA for selenium of 55 µg/day (~0.0008 mg/kg/day) (NAS 2000). The MRL does not represent a threshold for toxicity, but a daily intake that ATSDR considers to be safe for all populations. The exact point above the MRL at which effects might occur in sensitive individuals is uncertain.